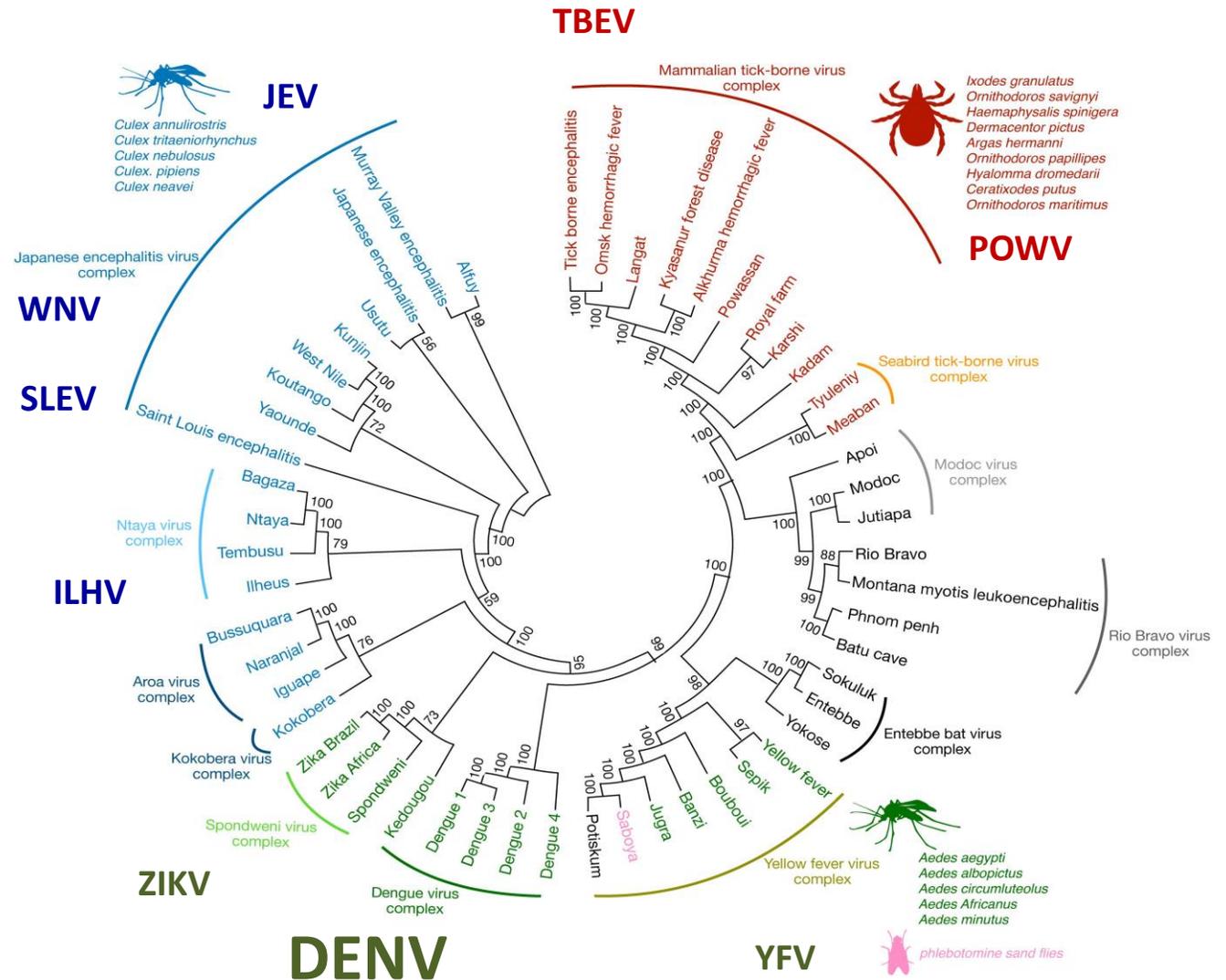


DENGUE VIRUS VACCINES

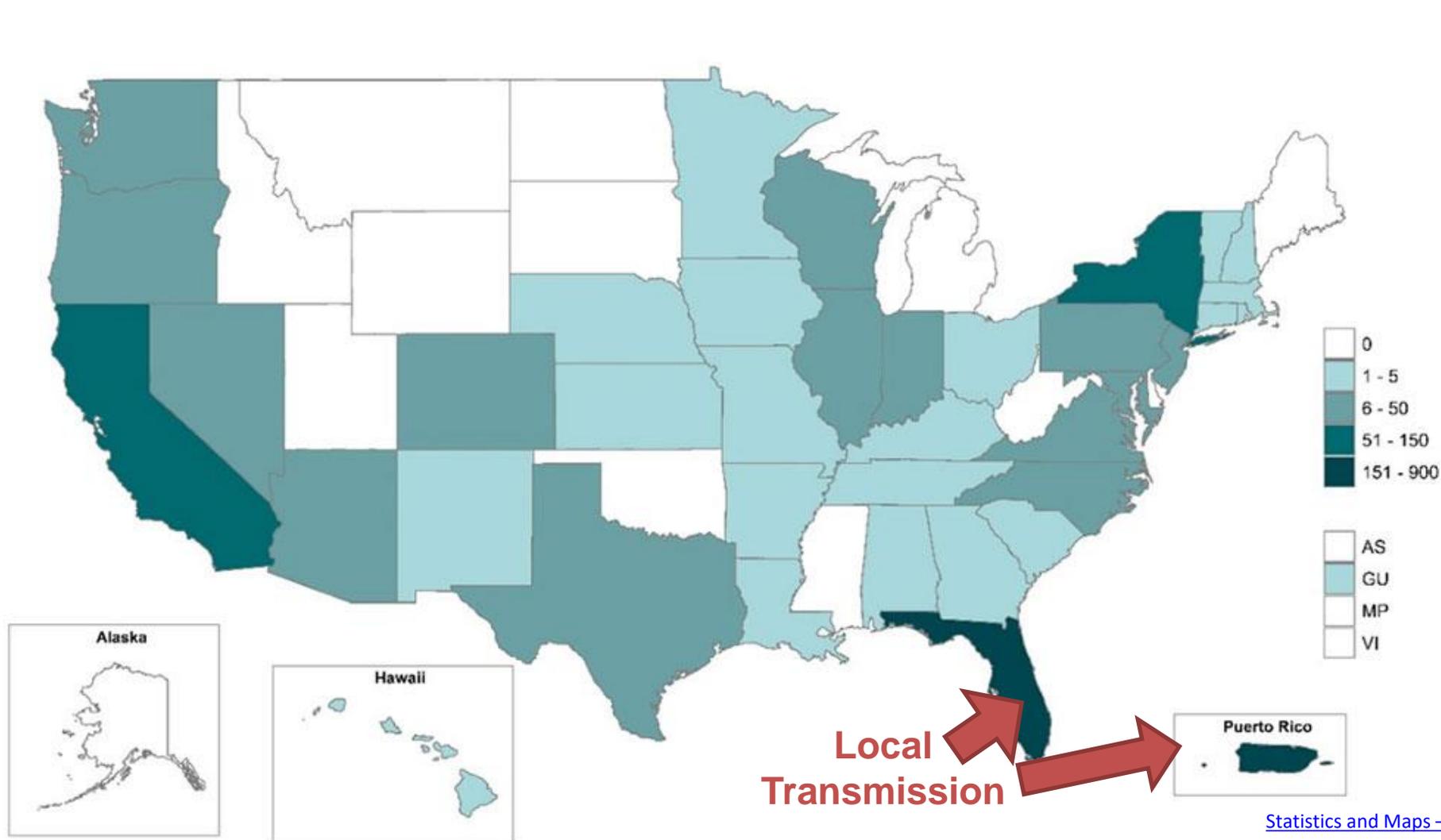
Kaitlyn M. Morabito, PhD
Program Officer, Flaviviruses
Virology Branch
DMID, NIAID, NIH

Dengue virus is a flavivirus that is transmitted by mosquito

Dengue Virus (DENV)



Most DENV cases in the USA are travel-related, but there is local transmission in Florida and US Territories



US States

- 1,188 dengue cases reported

US Territories

- 828 dengue cases reported

DENV infection typically causes a febrile illness

Symptoms of **DENGUE**



The most common symptom of dengue is high fever (40°C/ 104°F) usually accompanied by two or more of the following symptoms:



Headache



Pain behind the eyes



Nausea, vomiting



Swollen glands



Joint, bone or
muscle pains



Rash

DENV infection can advance to more severe disease

Symptoms of DENGUE



The most common symptom of dengue is high fever (40°C/ 104°F) usually accompanied by two or more of the following symptoms:



Headache



Pain behind the eyes



Nausea, vomiting



Swollen glands



Joint, bone or muscle pains



Rash

[Symptoms of dengue \(who.int\)](https://www.who.int)

Severe DENGUE



People who get sick with dengue may develop severe dengue which can be deadly. **WATCH OUT** for the warning signs and symptoms and seek immediate medical care if severe dengue is suspected.

- Severe abdominal pain
- Persistent vomiting
- Bleeding gums
- Vomiting blood
- Rapid breathing
- Fatigue/ restlessness

Paracetamol can be taken to bring down fever and pain. Avoid aspirin and ibuprofen.



[Severe dengue \(who.int\)](https://www.who.int)

Treatment for DENV is primarily supportive care

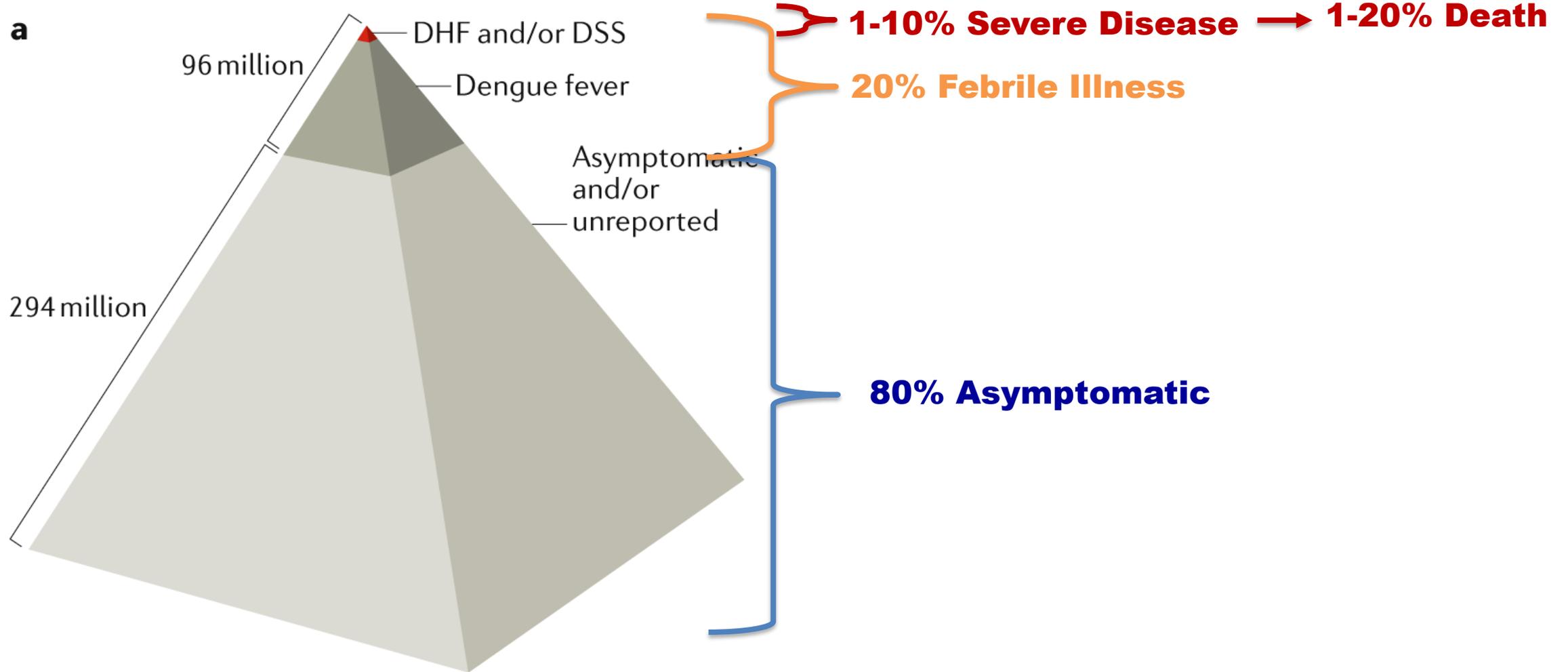
Oral or
IV hydration



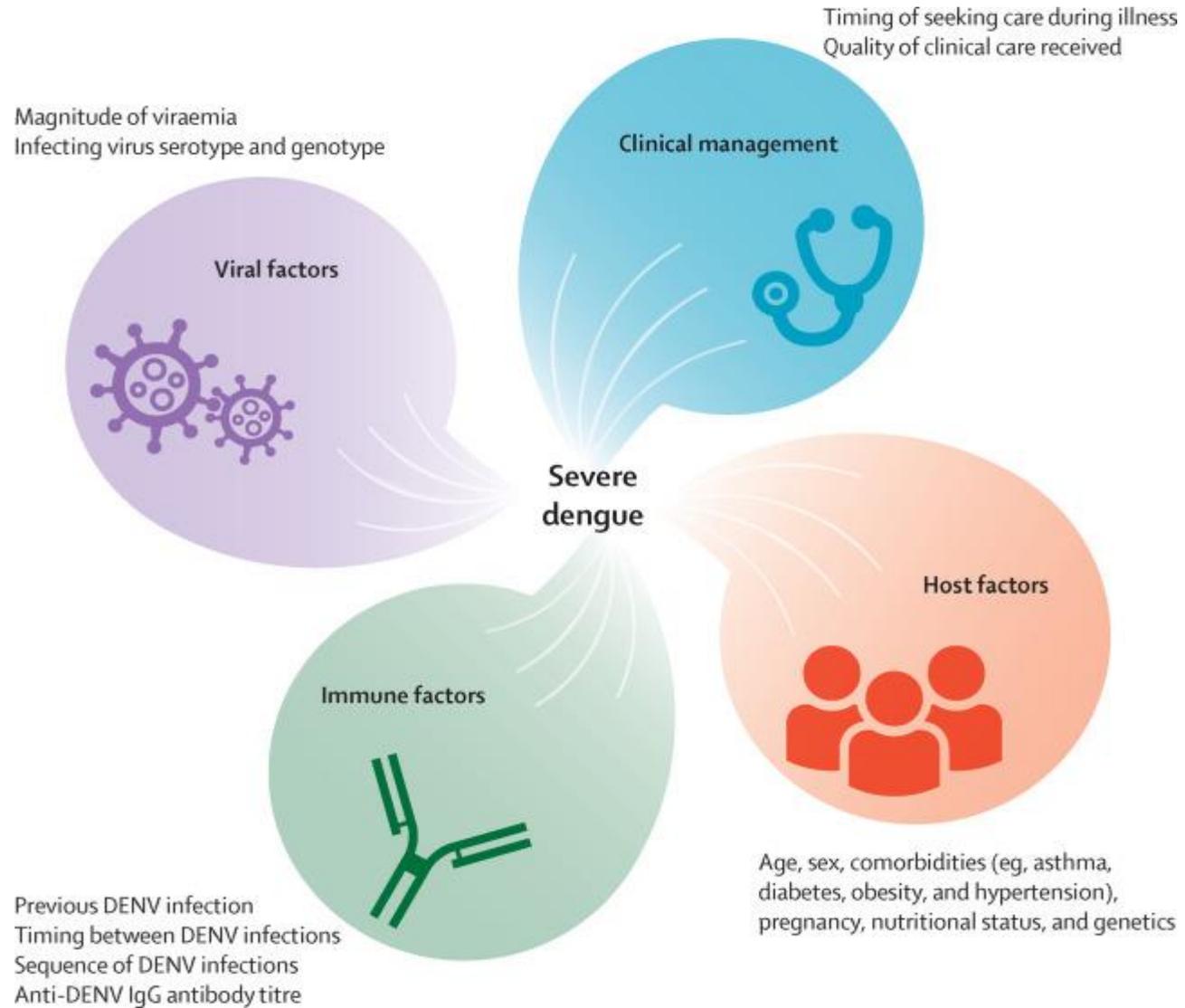
Fatality Rate

20%  1-2%

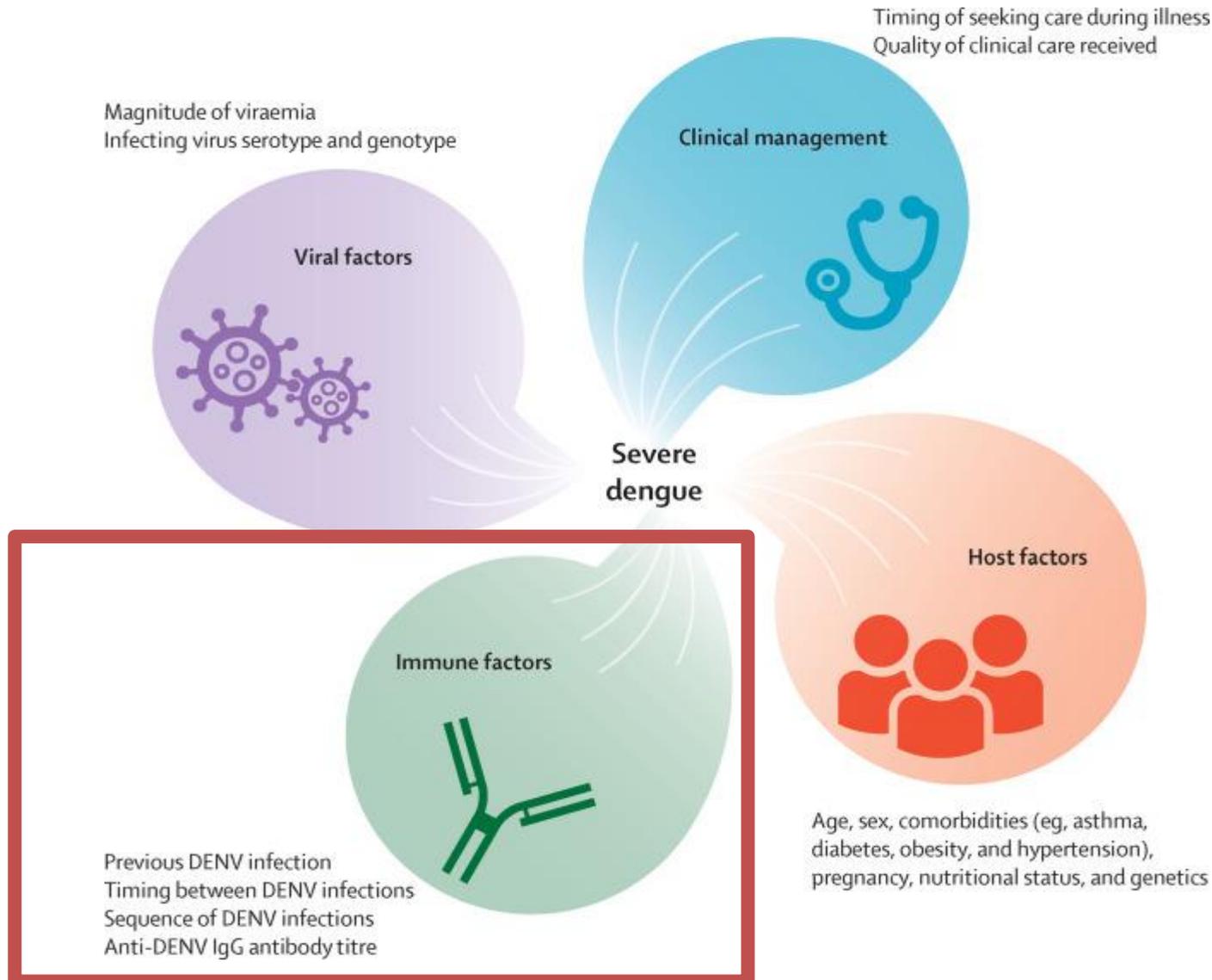
Only a small fraction of DENV infections lead to severe disease



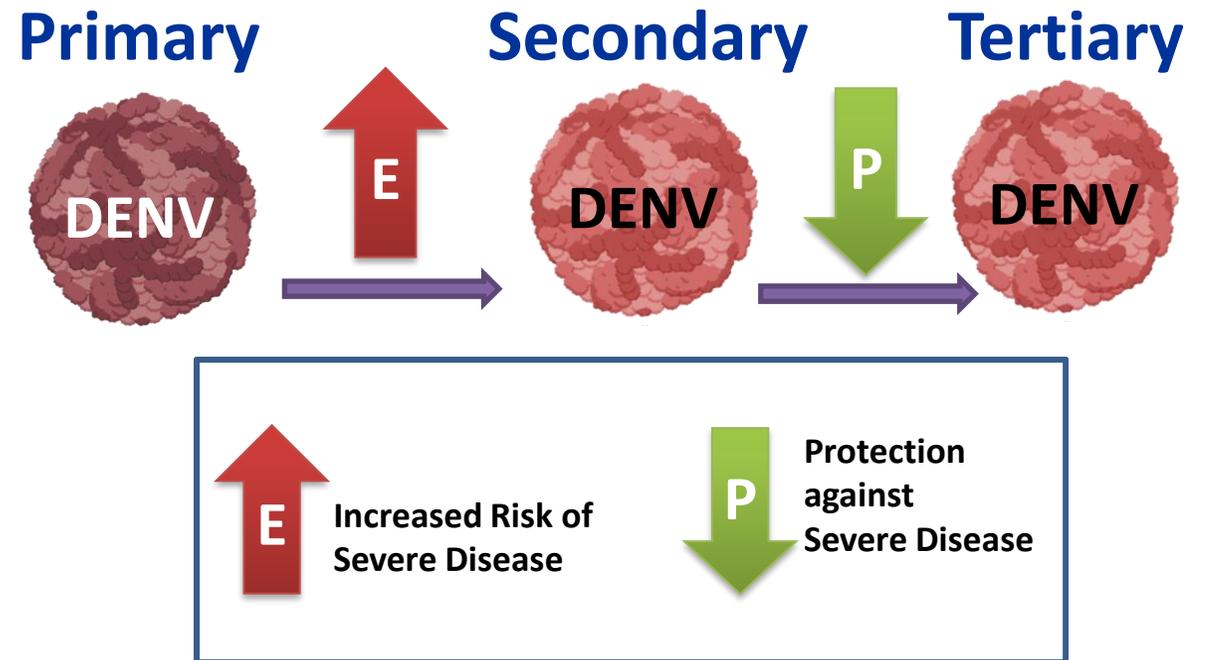
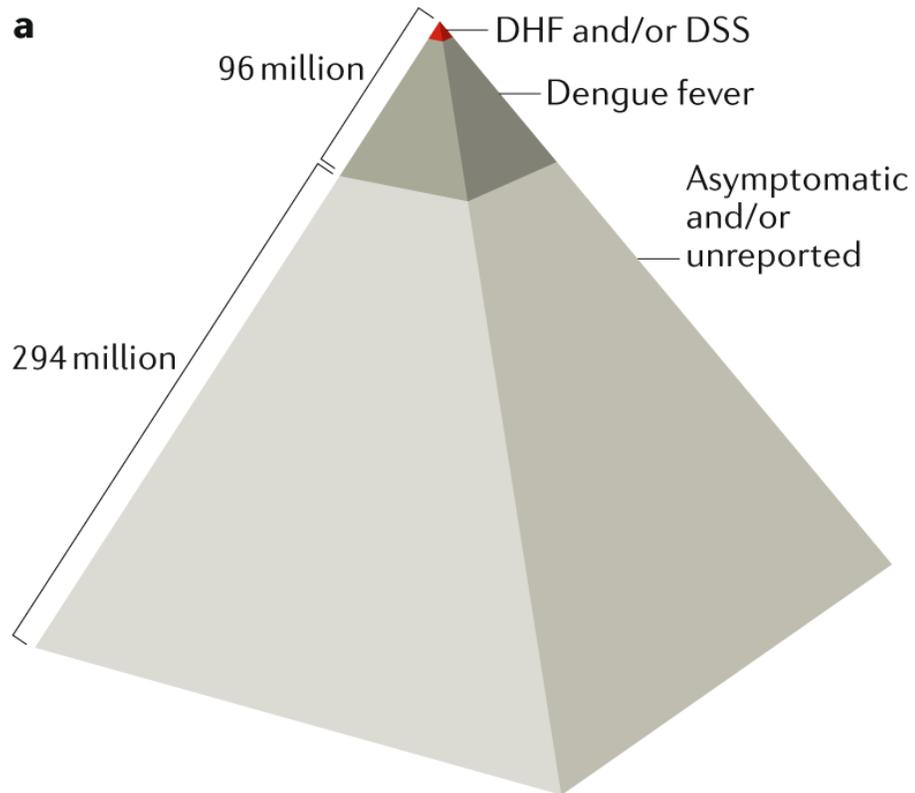
There are many factors that influence the clinical severity of dengue infection



Antibody-dependent enhancement has been a major challenge for development of DENV vaccines

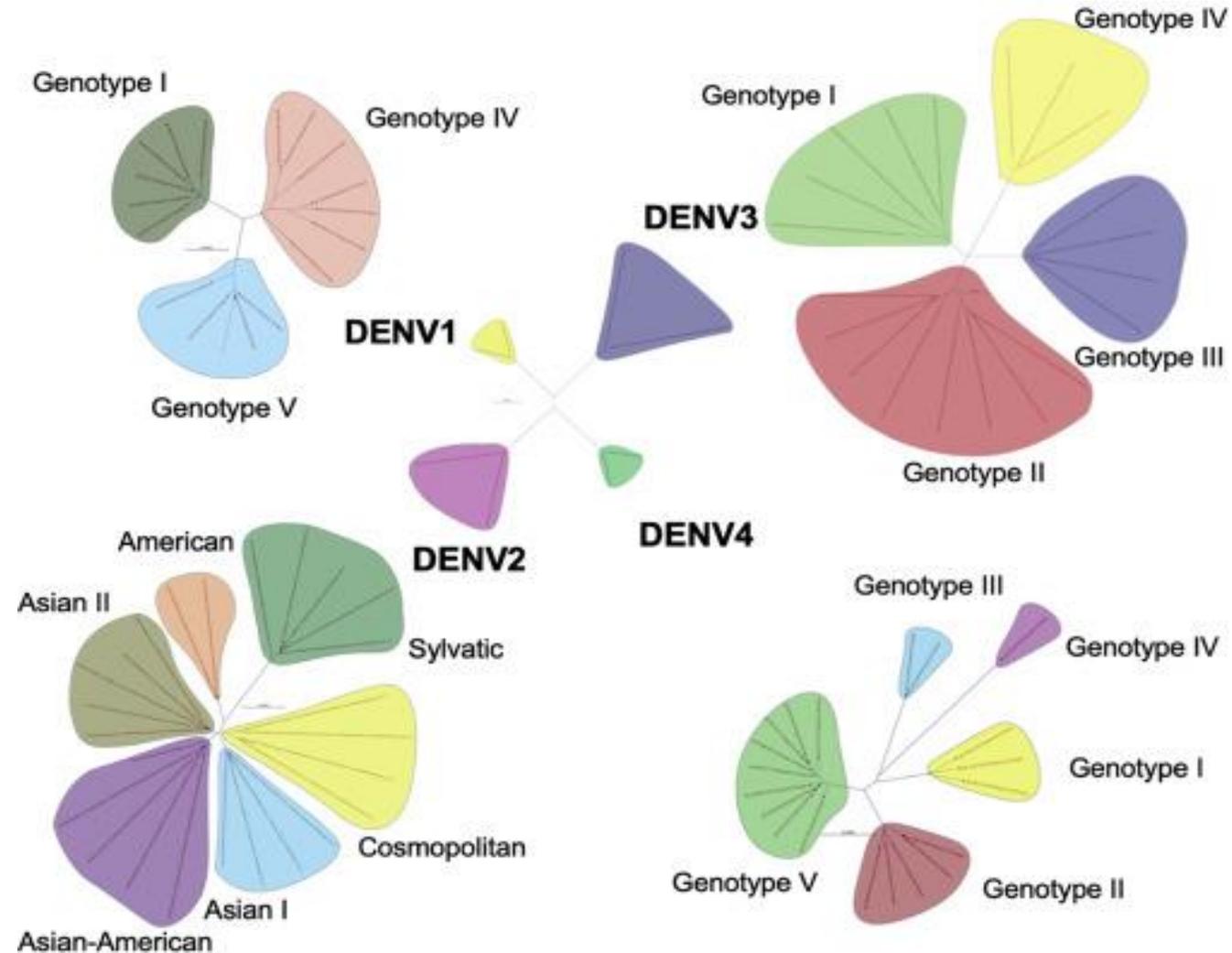


The risk of severe DENV disease increases upon secondary infection and decreases thereafter

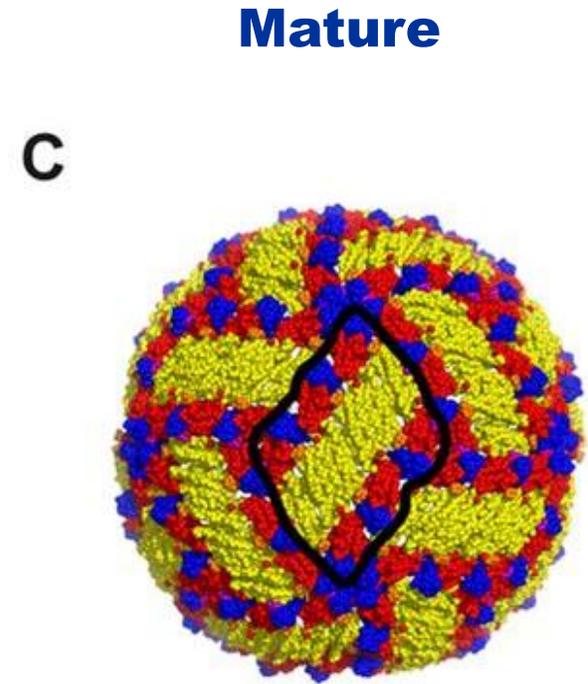
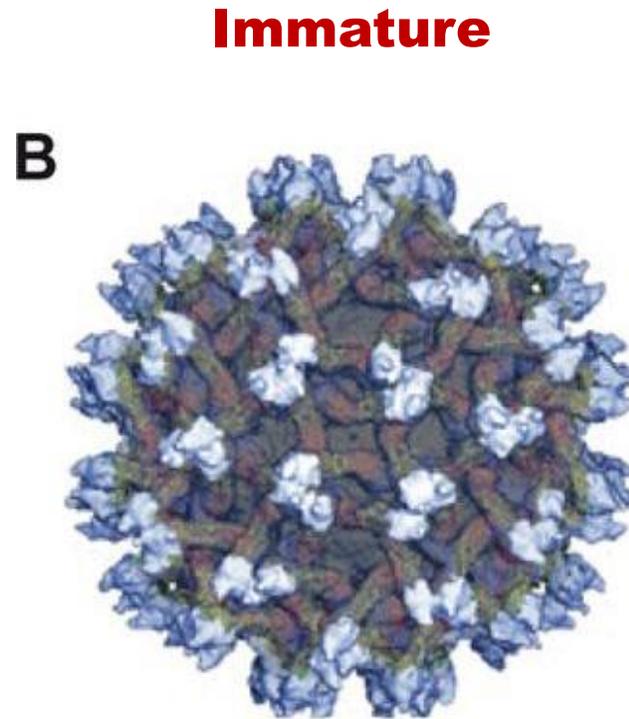
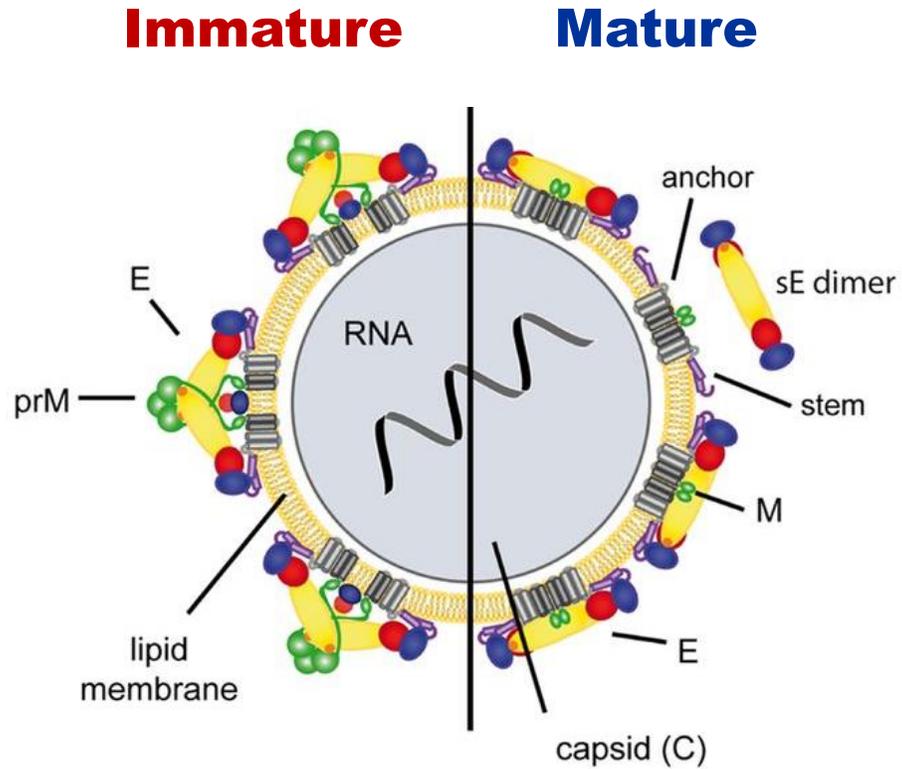


Phenomenon has been linked to antibody levels and referred to as **Antibody-Dependent Enhancement (ADE)**

DENV is a complicated target with 4 serotypes

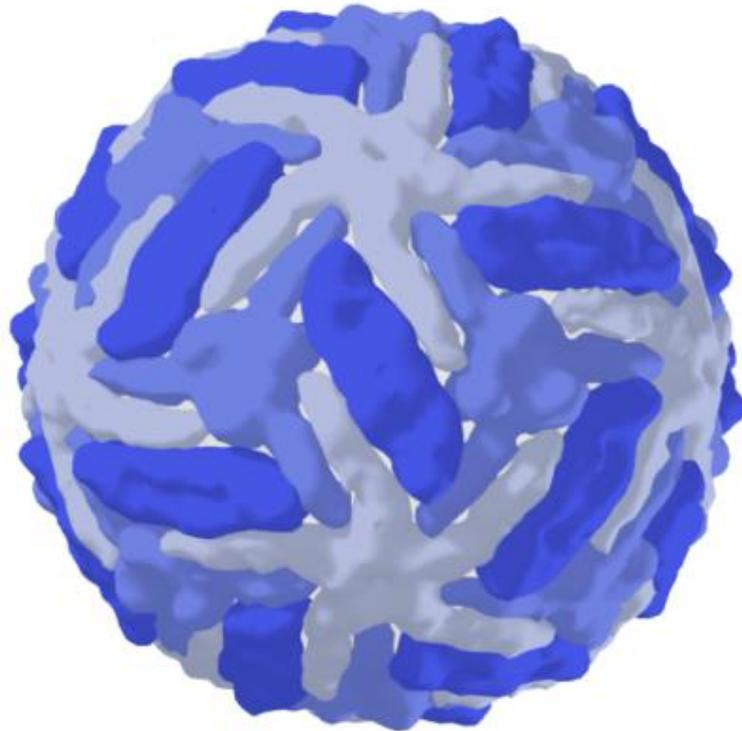


Flaviviruses take multiple forms



Flaviviruses are moving targets

Viral “Breathing”

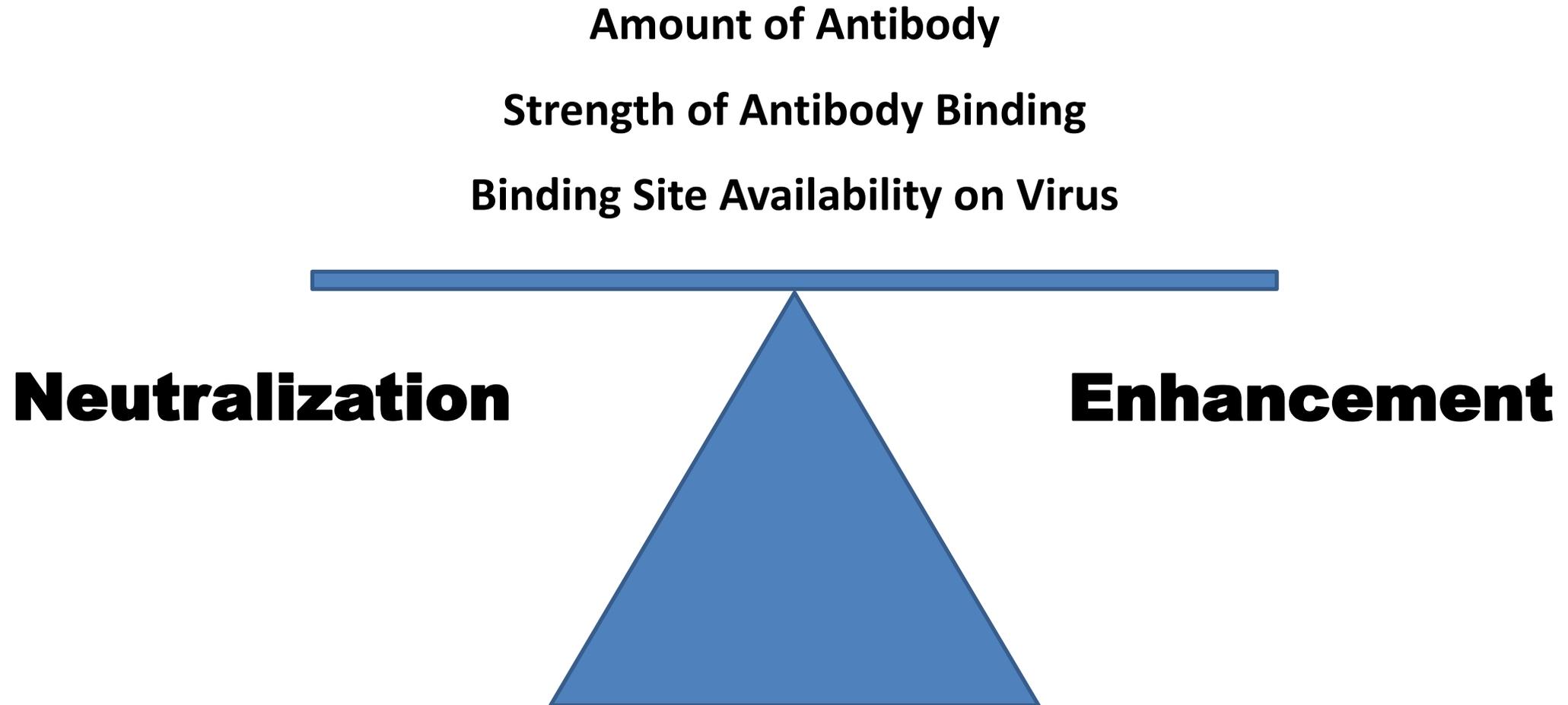


Flaviviruses are moving targets

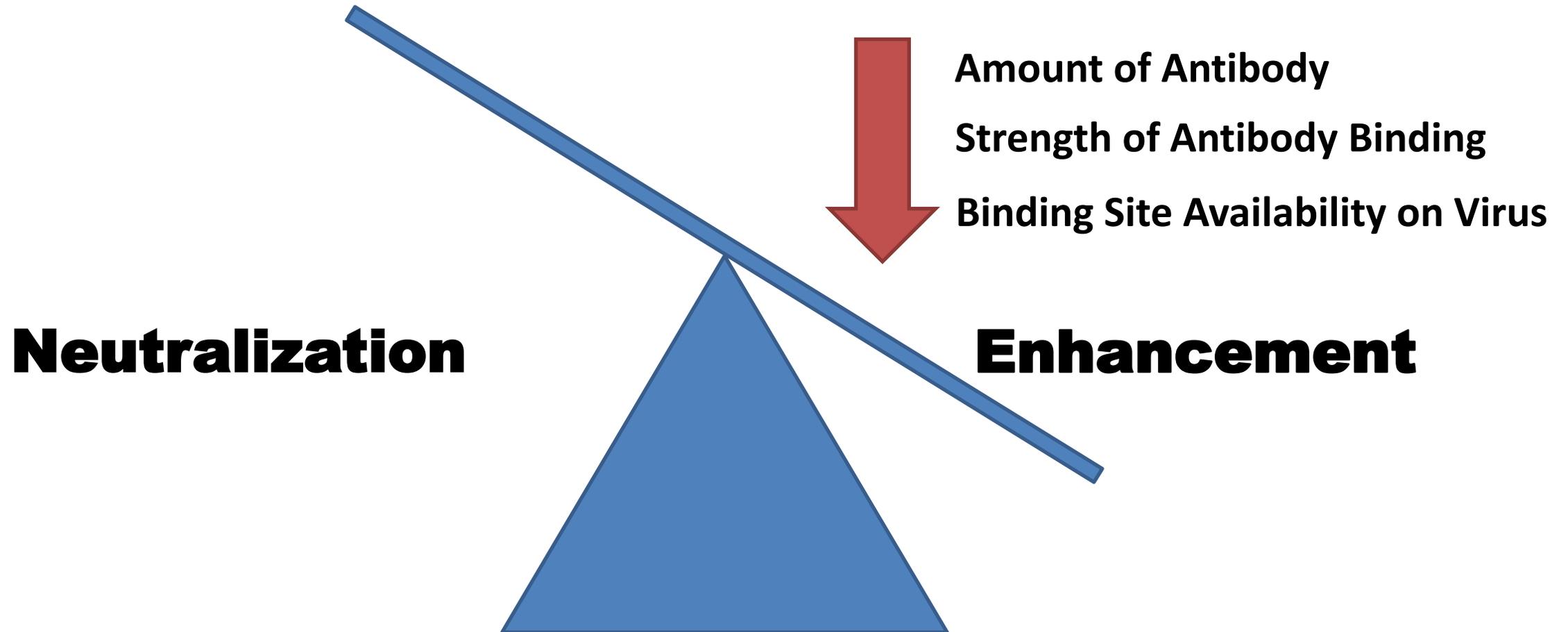
Viral “Breathing”

Recognition of these different forms is a high bar for antibodies

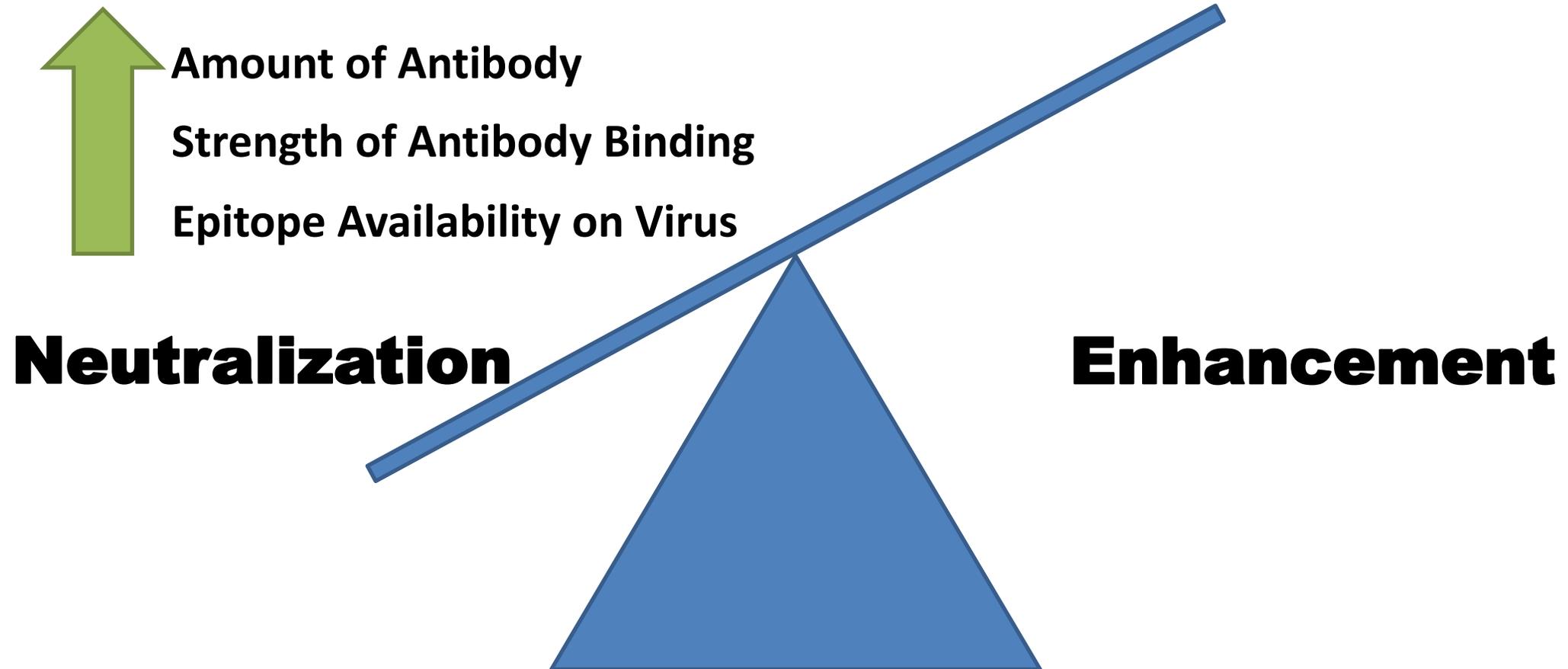
All antibodies can enhance, but poorly neutralizing antibodies have a higher potential for enhancement



All antibodies can enhance, but poorly neutralizing antibodies have a higher potential for enhancement

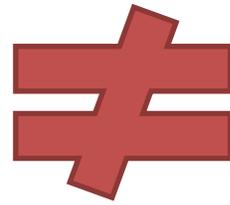


All antibodies can enhance, but poorly neutralizing antibodies have a higher potential for enhancement

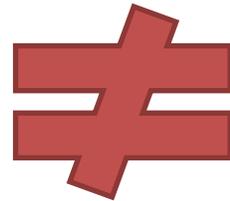
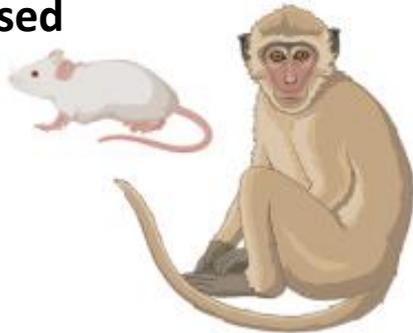


In vitro systems and animal models do not recapitulate human outcomes

False positives for enhancement in vitro



Immunocompromised mice



No Severe Disease

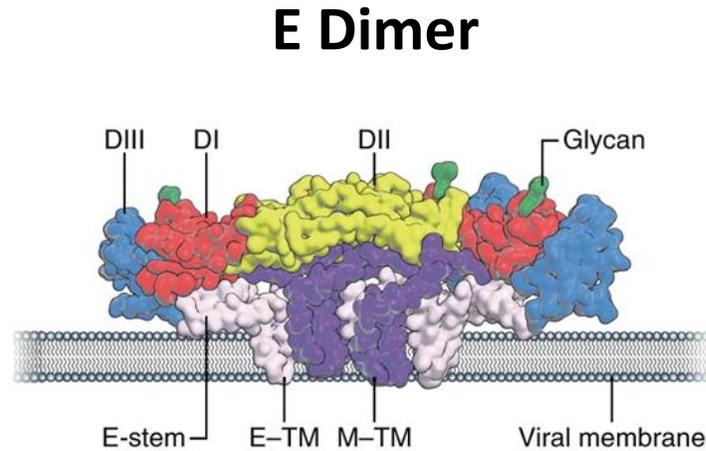


Despite the complexity, DENV vaccines will prevent significant illness and morbidity

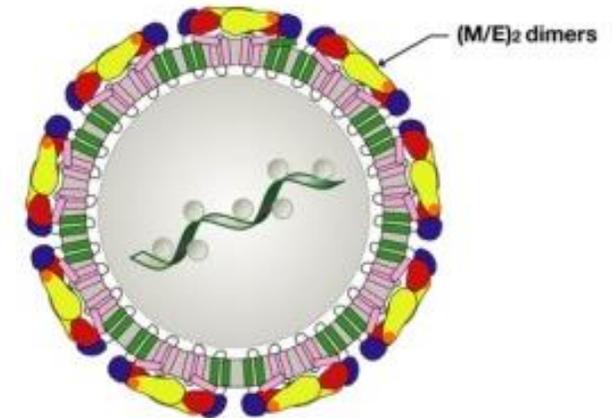
DENGUE VIRUS VACCINES

Flavivirus surface proteins are highly ordered and the major target of neutralizing antibodies

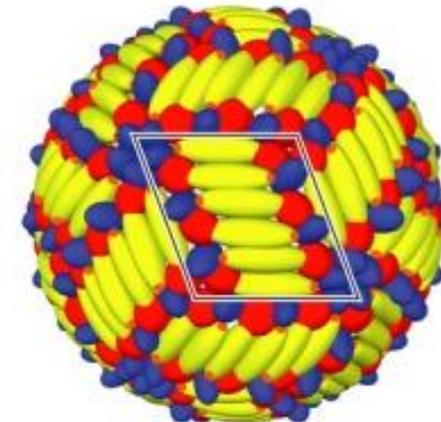
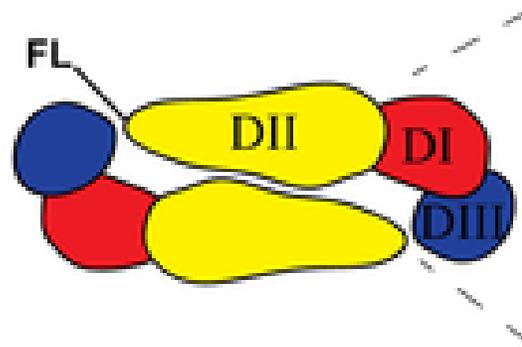
Side View



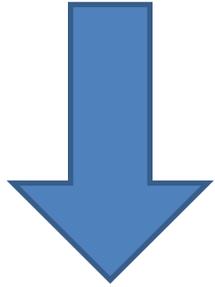
Virus Particle



Top Down



The most advanced DENV candidates are quadrivalent live-attenuated vaccines



Virus growth in people

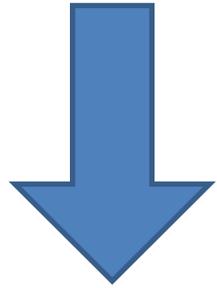


Do not cause disease



One for each serotype

The most advanced DENV candidates are quadrivalent live-attenuated vaccines



Virus growth in people



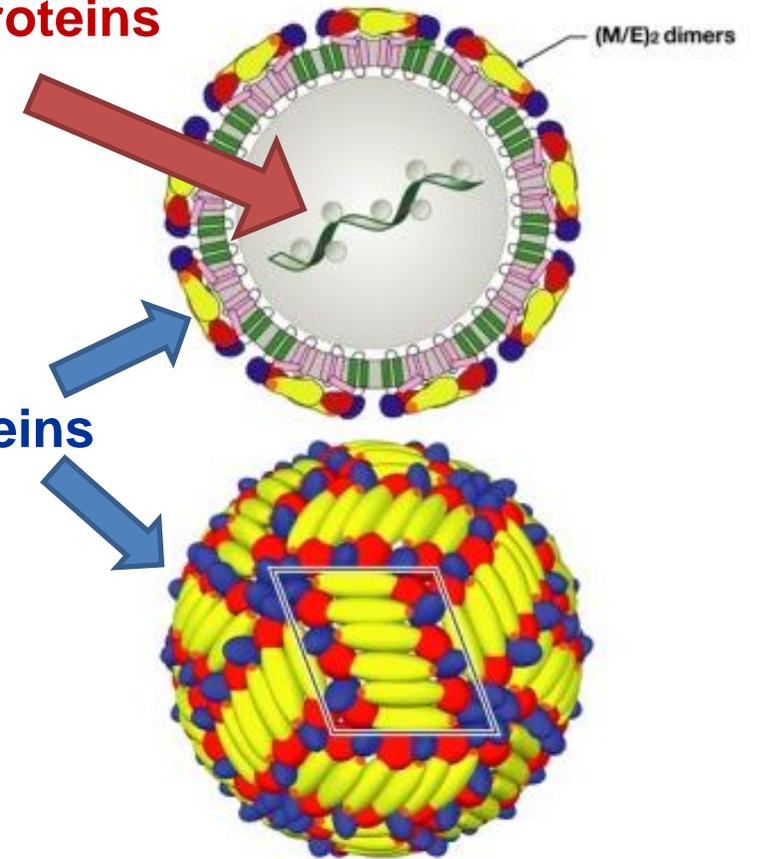
Do not cause disease



One for each serotype

**“Backbone”
Non-structural Proteins**

Surface proteins



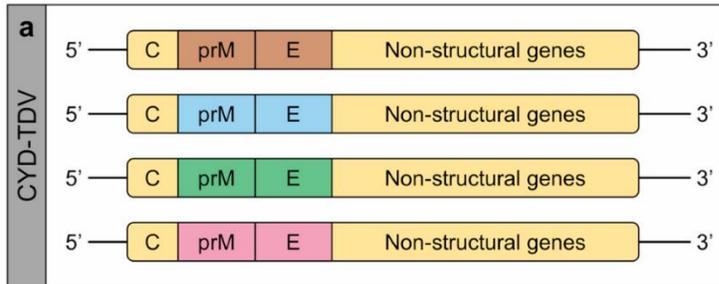
Looks like authentic virus to immune system

The 3 live-attenuated DENV vaccines use different backbones

Developer

Vaccine Design

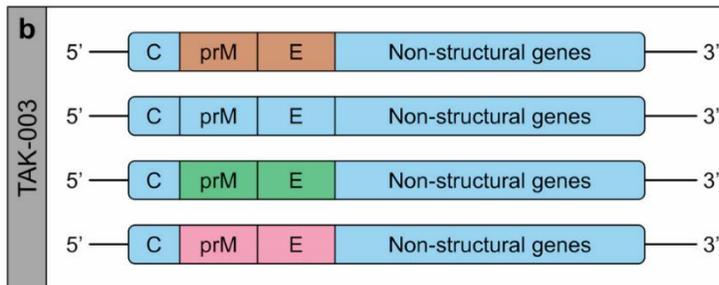
Backbone



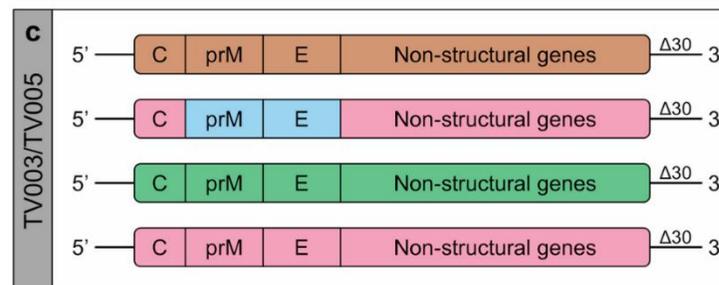
YFV



QDENGGA



DENV2



DENV1

DENV4

DENV3

DENV4

Dengvaxia elicits a different hierarchy of serotype-specific efficacy and enhances risk in seronegatives

Developer

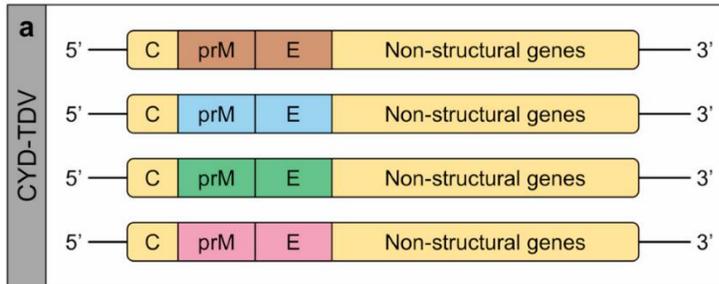
Vaccine Design

Backbone

Efficacy

Severe Disease

Current Status



YFV

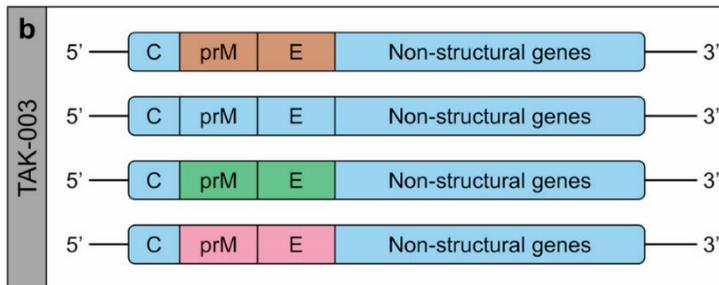
DENV4 – 77%
 DENV1 – 72%
 DENV3 – 55%
 DENV2 – 43%

Increased Risk in Seronegatives

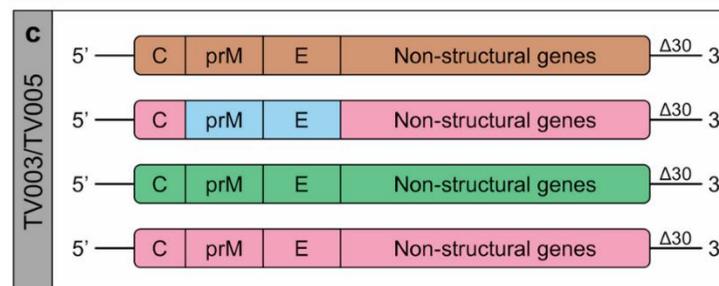
BLA
 ACIP rec'd
 9-16 yo Sero+



QDENGGA



DENV2



DENV1
 DENV4
 DENV3
 DENV4

Efficacy and safety of Dengvaxia differs between DENV naïve and DENV experienced people

Seronegative



DENV Naïve
No previous infection
No pre-existing antibody

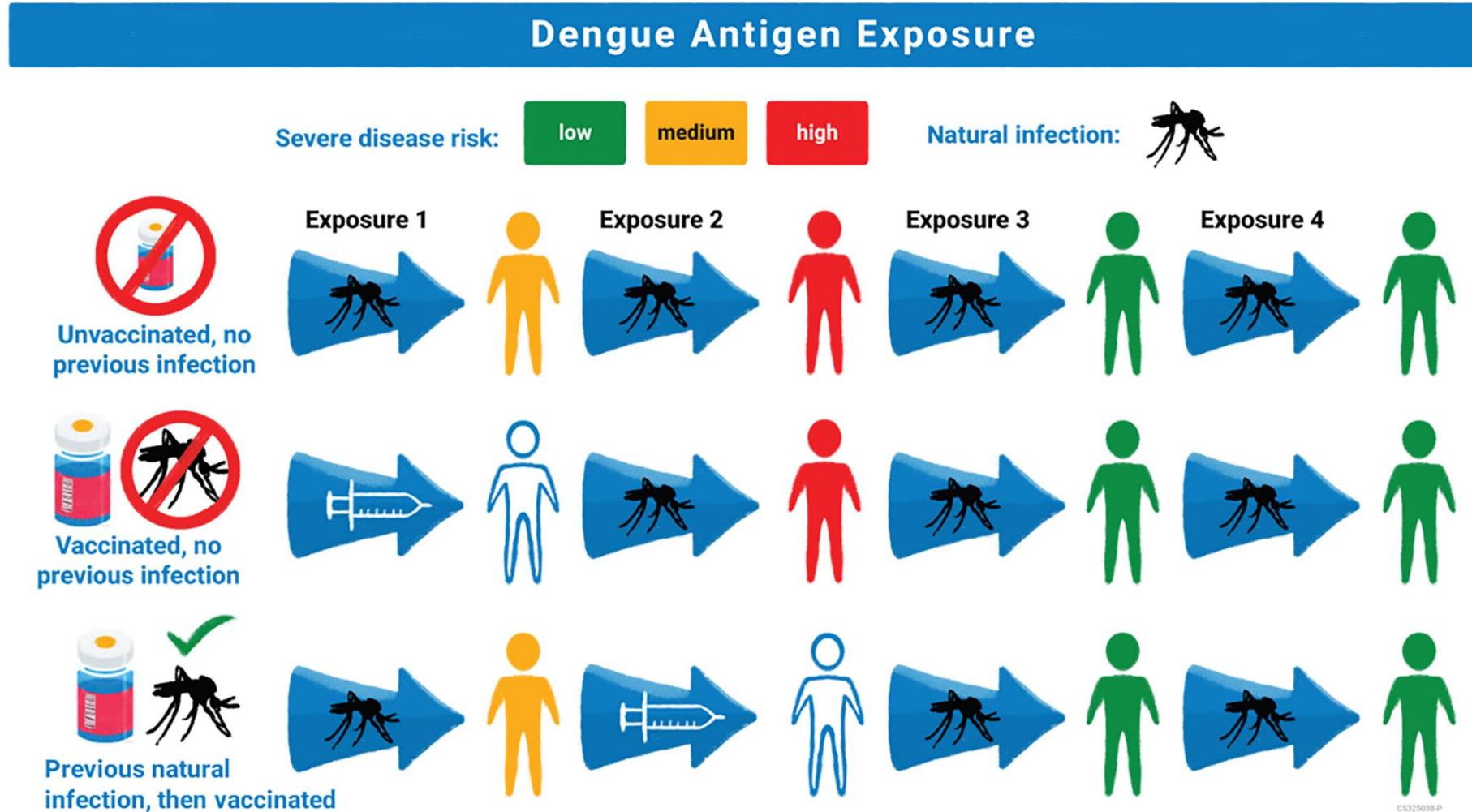
Seropositive



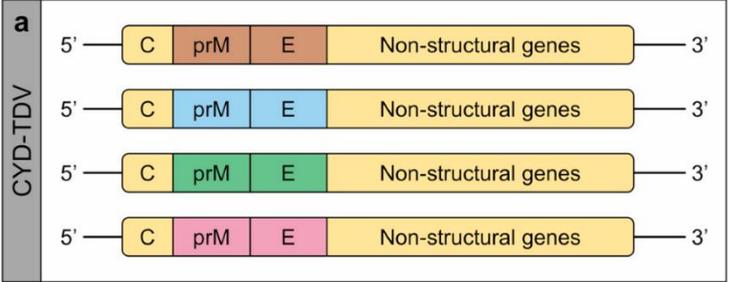
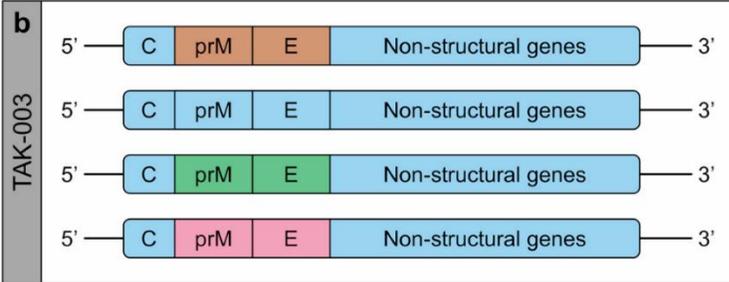
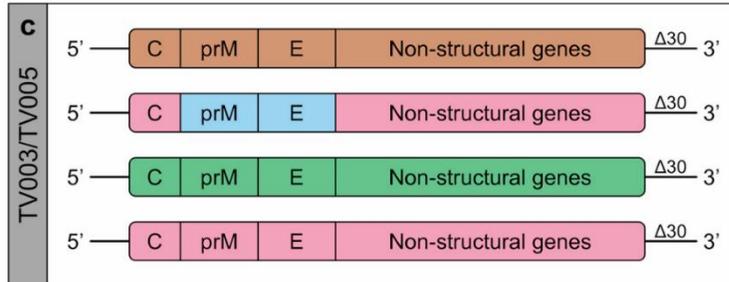
DENV Experienced
Previous infection
Pre-existing antibody

Safer
More Efficacious

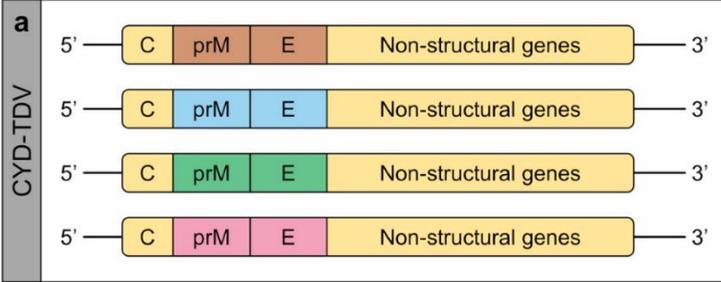
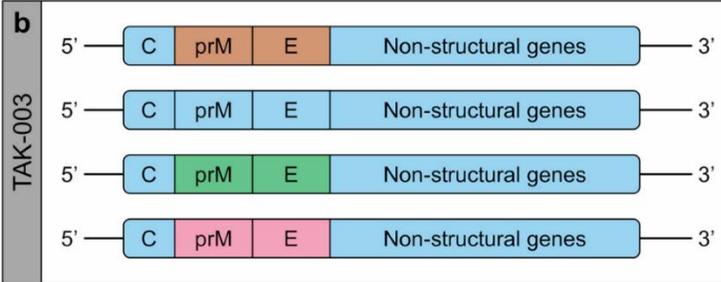
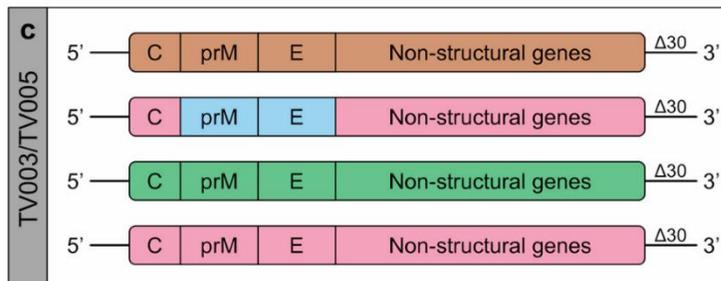
Dengvaxia vaccination of seronegative people acts like a first DENV Exposure



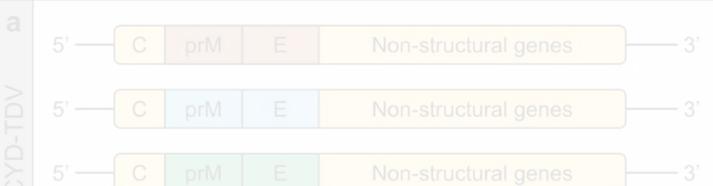
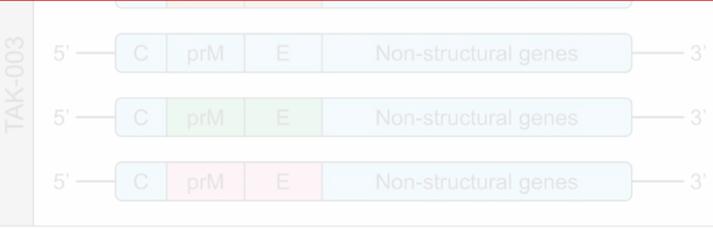
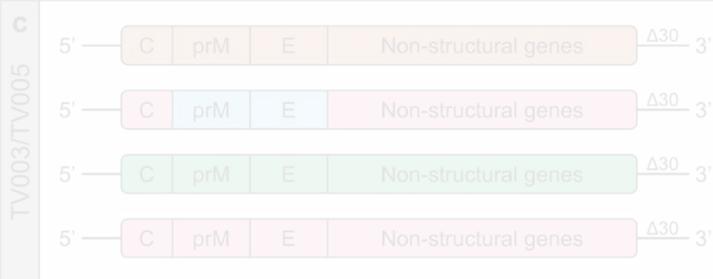
The live-attenuated DENV vaccines elicit a different hierarchy of serotype-specific efficacy

Developer	Vaccine Design	Backbone	Efficacy	Severe disease Disease	Current Status
 SANOFI Dengvaxia		YFV	DENV4 – 77% DENV1 – 72% DENV3 – 55% DENV2 – 43%	Increased Risk in Seronegatives	BLA ACIP rec 9-16 yo Sero+
 QDENGGA		DENV2	DENV2 – 95% DENV1 – 70% DENV3 – ?/None DENV4 – ?		Under FDA and ACIP Review
 National Institute of Allergy and Infectious Diseases   		DENV1 DENV4 DENV3 DENV4			

The live-attenuated DENV vaccines elicit a different hierarchy of serotype-specific efficacy

Developer	Vaccine Design	Backbone	Efficacy	Severe disease Disease	Current Status
 SANOFI Dengvaxia	a 	YFV	DENV4 – 77% DENV1 – 72% DENV3 – 55% DENV2 – 43%	Increased Risk in Seronegatives	BLA ACIP rec 9-16 yo Sero+
 QDENGGA	b 	DENV2	DENV2 – 95% DENV1 – 70% DENV3 – ?/None DENV4 – ?	?	Under FDA and ACIP Review
 National Institute of Allergy and Infectious Diseases   SERUM INSTITUTE OF INDIA	c 	DENV1 DENV4 DENV3 DENV4	?	?	Phase 3 Under Analysis

The live-attenuated DENV vaccines elicit a different hierarchy of serotype-specific efficacy

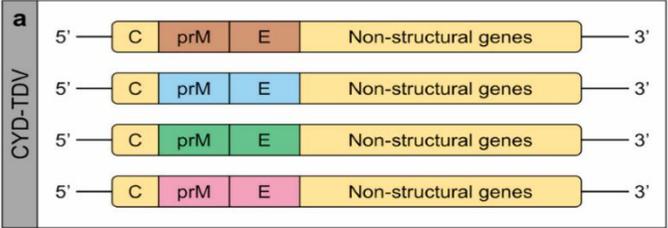
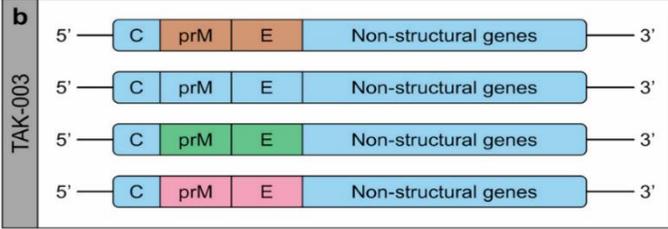
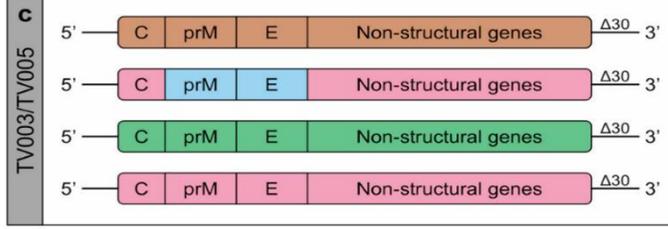
Developer	Vaccine Design	Backbone	Efficacy	Severe disease Disease	Current Status
		YFV	DENV4 – 77% DENV1 – 72%	Increased Risk in	BLA ACIP rec 9-16 yo Sero+
 QDENGGA		DENV2	DENV2 – 55% DENV1 – 70% DENV3 – ?/None DENV4 – ?	?	Under FDA and ACIP Review
 National Institute of Allergy and Infectious Diseases   		DENV1 DENV4 DENV3 DENV4	?	?	Phase 3 Under Analysis

Research is ongoing to dissect immune responses to these vaccines to better understand protection

Key Take-aways

- Severe DENV infection is rare but serious
 - Severity of DENV infection is multifactorial
 - Including complex antibody response
- DENV vaccines prevent significant morbidity
- Live-attenuated DENV vaccines are Safe and Efficacious in Seropositives
- Safety and efficacy are less clear for Seronegatives, and will need to be evaluated for each vaccine

Questions?

Developer	Vaccine Design	Backbone	Efficacy	Severe disease Disease	Current Status
	<p>a</p> 	YFV	<p>DENV4 – 77%</p> <p>DENV1 – 72%</p> <p>DENV3 – 55%</p> <p>DENV2 – 43%</p>	<p>Increased Risk in Seronegatives</p>	<p>BLA ACIP rec 9-16 yo Sero+</p>
	<p>b</p> 	DENV2	<p>DENV2 – 95%</p> <p>DENV1 – 70%</p> <p>DENV3 – ?/None</p> <p>DENV4 – ?</p>	?	<p>Under FDA and ACIP Review</p>
	<p>c</p> 	<p>DENV1</p> <p>DENV4</p> <p>DENV3</p> <p>DENV4</p>	?	?	<p>Phase 3 Under Analysis</p>